termined and chylomicron tests should be obtained before prescription of oral contraceptives. If abnormalities are found, other types of birth control devices should be evaluated, considering in each case the risk of pregnancy versus the risk of severe hyperlipidemia. If contraceptive steroids are utilized, only the smallest dose of estrogens should be used and close follow-up with periodic measurement of plasma lipids is necessary.

Complications of Systemic Contraceptive Agents: Hypertension

ADA R. WOLFSEN, MD*

INCREASED BLOOD PRESSURE associated with oral contraceptive therapy was first reported by Owen in 1966.[106] Laragh et al in 1967[107] reported a temporal relationship between the initiation of oral contraceptive therapy and the onset of systolic and diastolic hypertension in six of eleven patients. He also observed improvement or correction of hypertension after withdrawal of the medication.

Prospective studies by Tyson,[108] Saruta[109] and Clezy[110] indicated a 15.5 percent, 18 percent and 4.05 percent incidence, respectively, of sustained systolic and diastolic hypertension with oral contraceptive therapy. The lower incidence of hypertension in Clezy's study was attributed to different diagnostic criteria and difference in the population studies. Women who remained normotensive during therapy also had a small significant increase in systolic blood pressure.

Spellacy and Birk reported a similar occurrence of hypertension ranging from 5 percent to 7 percent in oral contraceptive users, in those taking ethinyl estradiol and in those taking mestranol, whereas hypertension was not found in women using intrauterine devices, progestogens or conjugated estrogens.[111] This study showed the estrogen component of combined oral contraceptives was the important agent for the development of hypertension.

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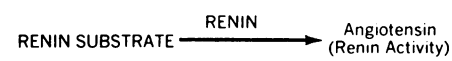
RENIN CONCENTRATION



RENIN SUBSTRATE:	Amount angiotensin generated by additional excess renin
RENIN ACTIVITY:	Amount angiotensin generated by entire system, without additions
RENIN CONCENTRATION:	Amount angiotensin generated in presence of fixed amount of renin substrate

Chart 12.—Components of the renin-angiotensin system. (Reproduced by permission from Saruta T, et al: Arch Intern Med 126:621, 1971, "Copyright 1970, American Medical Association")

During estrogen therapy an increase in renin substrate, resulting in activation of the renin-angiotensin system, has been observed. It is currently believed that renin, secreted by the juxtaglomerular cells, cleaves circulating renin substrate, an alpha 2 globulin synthesized in the liver to form the decapeptide angiotensin I which is rapidly cleaved predominantly in the lung, producing angiotensin II. The actions of angiotensin II include contraction of smooth muscle, stimulation of aldosterone secretion and suppression of renin release by the kidney. Angiotensin II is rapidly metabolized in the vascular bed, having a half life of about 1 minute.[112]

Chart 12 summarizes the methods of measurement of the various components of the renin-angiotensin system. Renin substrate is the amount of angiotensin generated by additional excess renin. Renin activity is the amount of angiotensin generated by the entire system without additions. This reflects endogenous renin substrate and the amount of renin circulating. Renin concentration is the amount of angiotensin generated in the presence of a fixed amount of renin substrate.

The changes in the components of the renin-angiotensin system in 13 women who remained normotensive on combined oral contraceptive therapy were reported by Cain et al.[113] There were pronounced elevations of angiotensin II observed within five days of the beginning of therapy. There were less pronounced increases in plasma renin substrate and renin activity. Plasma renin concentration was suppressed during oral contraceptive therapy; this was attributed to the inhibition of renin secretion by increased levels of angiotensin II. All values returned to the normal range one month after withdrawal of treatment, and fell below the normal mean one month later.

Similar changes in the renin-angiotensin system have been observed by Helmer and Griffith in

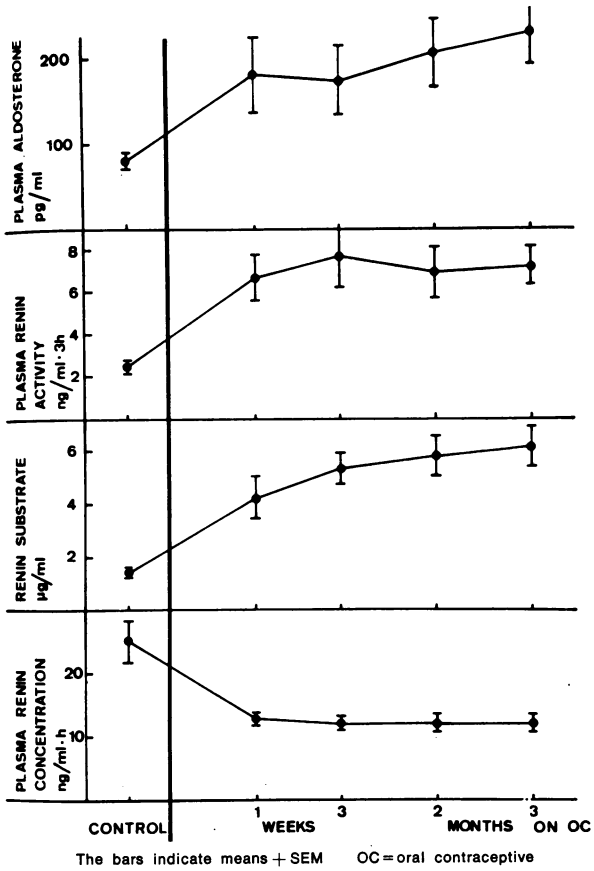


Chart 13.—Changes in plasma aldosterone, plasma renin activity, plasma renin substrate, and plasma renin concentration during the first 3 months of contraceptive therapy. (Reproduced by permission from Beckerhoff R, et al: Lancet 1:1218, 1973)

estrogen-treated rats; estrogen treatment caused a rapid increase in plasma renin substrate.[114] This was followed by increased plasma renin activity and decreased plasma renin concentration. This ability to increase renin substrate appeared to be a common property of all the estrogens tested.

Chart 13 illustrates the changes in plasma aldosterone, renin activity, renin substrate and renin concentration induced by oral contraceptive therapy in ten normal women reported by Beckerhoff.[115] Mean plasma aldosterone before treatment was 83 pg per ml; this rose to 183 pg per ml within one week of therapy, and to 229 pg per ml after three months of therapy. Mean plasma renin activity increased 268 percent, renin substrate increased 339 percent and renin concentration fell 50 percent within one week. These women gained an average of 1 kg in body weight during the time of observation. This was attributed to salt and water retention from increased aldosterone activity. Mean blood pressure was 105/72 mm of mercury before therapy and 106/73 after three months of therapy, indicating that the activation of the renin-angiotensin-aldosterone system was well compensated.

Hemodynamic changes in normotensive women on oral contraceptives were reported by Cain et al.[113] Average cardiac output increased significantly by 1.07 liters per minute; blood volume increased 454 ml and body weight increased 1.14 kg. These changes were associated with a significant increase in mean systolic blood pressure of 3.4 mm of mercury, an increase in mean diastolic pressure of 1.5 mm and a rise in mean blood pressure of 2.4 mm.

It has been suggested that hypertension may result from failure of the negative feedback suppression of renin secretion which normally minimizes the increase in renin activity resulting from increased renin substrate concentration. Saruta,[109] in a prospective study, reported renin substrate and renin concentration levels were higher in women who became hypertensive on oral contraceptives than in those who remained normotensive. However, there was no significant difference in renin activity in the normotensive compared with the hypertensive group. Therefore, there is no evidence for a defective feedback mechanism in the women who become hypertensive with oral contraceptive therapy.

Beckerhoff's study of 11 women in whom hypertension developed while they were taking oral contraceptives suggested that a profound decrease in plasma renin concentration during therapy was associated with reversibility of the hypertensive state when therapy was discontinued, whereas less profound suppression of plasma renin concentration was associated with sustained hypertension after therapy withdrawal.[116]

Since changes in the renin-angiotension-aldosterone system are not significantly different in the women who become hypertensive than in the women who remain normotensive on oral contraceptives, other factors have been postulated as causes of the hypertension. Changes in angiotensin II metabolism or minimal renal disease have been postulated but have not been documented in the women in whom estrogen-induced hypertension develops. There is some evidence of a genetic predisposition to hypertension in the women who become hypertensive with estrogen therapy. Spellacy and Birk found a 38 percent frequency of hypertension in women who had previously had hypertension during pregnancy, compared with a

9 percent frequency in women with a negative history.[111] Clezy reported a 58 percent incidence of hypertension on at least one visit in women with a positive history of hypertension during pregnancy, compared with a 23 percent incidence in women with a negative history.[110] He also observed a 53 percent incidence of hypertension on one or more visits during oral contraceptive therapy in women with a parental history of hypertension compared with a 30 percent incidence in those with a negative family history.

It seems likely that the estrogen-induced changes in the renin-angiotension-aldosterone system act on the background of genetic predisposition for hypertension, to produce significant hypertension in a small percentage of persons.

Liver Disease and Abnormalties of Laboratory Tests

DELBERT A. FISHER, MD*

THE STEROID HORMONES in contraceptive preparations exert a number of metabolic effects on the liver. In addition to the alterations in carbohydrate and lipid metabolism already discussed, these hormones modify the rate of synthesis and secretion of a variety of plasma proteins, particularly those that bind hormones and metal ions. The protein most thoroughly studied is thyroxine binding globulin (TBG), an interalpha globulin which is the primary carrier protein for thyroid hormones in serum. The administration of estrogens to euthyroid subjects results in increased serum concentrations of TBG, with the result that serum thyroxine and triiodothyronine concentrations increase. Free hormone concentrations, however, are unchanged after equilibrium is reestablished and hormone production rates remain unchanged.[117-120] In contrast, androgenic hormones and a number of synthetic progestational agents, including norethandrolone and methandrostenolone, reduce serum TBG and thyroid hormone concentrations, also without altering free thyroxine concentrations or thyroid hormone turnover rates.[120-123] These changes in TBG concentration which occur with estrogen or androgen administration are associated with reciprocal changes in the plasma levels of thyroxine binding prealbumin (TBPA).[123]

During therapy with oral contraceptive agents combining estrogen and a progestational steroid, the effect of estrogen on TBG synthesis predominates; that is, a significant increase in serum TBG concentration occurs.[119,124] However, there is no change or an actual increase in serum TBPA concentration.[124,125] It is presumed that these changes reflect changes in synthesis and secretion of these carrier proteins by the liver, since degradation rates are not altered.[123]

More recently, estrogen has been shown to increase plasma concentrations of corticosteroid binding globulin, testosterone-estradiol binding globulin and ceruloplasmin (copper binding protein),[126-128] and these binding protein levels as well as serum levels of transferrin (iron binding protein) and transcobalamin (vitamin B_{12} binding protein) are increased in women taking contraceptive steroid hormone preparations containing estrogen and a progestational agent.[125,129-134] In this regard, administration of these drugs stimulates the changes in serum protein concentrations observed during pregnancy. The increases in these binding protein concentrations result in increased serum levels of the bound hormones, metals or vitamins, but, by analogy with the normal thyroid hormone turnover rates in patients with increased TBG levels, turnover rates and body economy of the hormones, metals, or vitamins are thought to be unchanged.

Increased concentrations of a second group of plasma proteins also occurs; these act as precursors of more active compounds by serving as substrates for a series of enzyme systems. They include angiotensinogen (or renin substrate), plasminogen and fibrinogen.[125,132] Plasma levels of alpha antitrypsin, $beta_{1c}$ globulin, hemopexin and $alpha_2$ macroglobulin also tend to increase, whereas plasma concentrations of the acute phase reactants, orosmucoid and haptoglobulin, decrease; serum albumin concentrations increase slightly if at all.[125,129,132] These changes in serum protein concentrations are summarized in Table 19.

The levels of beta lipoproteins tend to increase and are discussed more fully in the section dealing with serum lipid alterations. The changes in renin substrate are discussed under hypertension.

All of these effects presumably are due to the

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